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Review Of Neurotechnological Interventions: A Need For A Recommended Public Health Response

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Abstract

After preliminary review of relevant research articles, the thesis was able to gain a deeper understanding of neurotechnological interventions (e.g. deep brain stimulation, and other neurostimulators), specifically in regards to their use in treatment of motor conditions (e.g. Parkinson's, Epilepsy, etc.) and for some psychological disorders (e.g. depression, other mood disorders, etc.). A scoping review was conducted on a specific class of treatments used for particular conditions: invasive neurotechnological treatments for mood disorders. The reasoning behind this specified approach was due to the lack standardized policies and regulations in place for invasive neurotechnological interventions used for treatment of mood disorders – in contrast to more policies and regulations for non-invasive interventions. Therefore, the scoping review will attempt to cover research available based on other certain attributes, such as: current regulations (e.g. FDA guidelines and CMS rules), economic considerations, and any legal or ethical implications. Last, from such review, the thesis will attempt to propose a recommended public health response to these treatments. It is hoped that adoption of public health safeguards can ensure ethical and effective application of invasive neurotechnological treatments for mood disorders.

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Introduction

Background

There is a growing use of neurostimulators and other neurotechnological interventions as treatment for severe neurological ailments, typically as a last resort option for severe motor or mood disorders, such as Parkinson's disease or treatment-resistant depressive disorder(Edwards C, 2017). Neurostimulators can be defined as "active implantable devices that provide therapeutic intervention, sensory feedback or improved motor control via electric stimulation of neural or neuro-muscular tissue in response to trauma or disease."(Shephard, R.L, 2018). For the purposes of the thesis, neurostimulators will be used interchangeably with 1) neurotechnological interventions, 2) neuromodulation techniques, and 3) neurostimulation treatments or devices. Mood disorders will be used as a synonymous term for 'psychiatric disorders.' Mood disorders can encompass, but not be limited to 1) Treatment-Resistant Depression (TRD), 2) General Anxiety Disorder (GAD), and 3) Obsessive Compulsive Disorder (OCD). Addiction disorders and others substance-related disorders may also be included when necessary.

Common examples of invasive treatments used in treatment for mood disorders are Deep Brain Stimulation (DBS) and Vagal Nerve Stimulation (VNS). (Wong, 2018). Other invasive neurostimulation techniques are "motor cortex stimulation (MCS), responsive neurostimulation (RNS), and spinal cord stimulation (SCS)" – but only have therapeutic use with movement disorders, not mood disorders(Edwards C, 2017). Since most neurostimulators can be medical devices, they are also classified by federal regulatory bodies like the Food and Drug Administration (FDA)(Rome, 2014). The FDA classifies medical devices based on their

respective risk level, with devices with lower risk levels belonging to Class I and II, and thus have "simple requirements for getting to the market" versus devices tiered into Class III (Shepard R, 2018). Implantable devices are considered to be implantable neurostimulators and are an example of Class III devices. Thus, they will typically have longer testing requirements due to a more stringent regulatory pathway which imposes additional testing (O'Neill T, 2019).

In contrast, non-invasive neuromodulation devices are not surgically implanted into the patient (like they are in invasive treatments); thus, they are not 'implantable' medical devices (Wong, 2018). Rather, non-invasive neurostimulation is the "process or technology that applies electrical currents, in varying parameters, by.... inhibition of specific neuronal groups, pathways, or networks." (Edwards C, 2017). Examples include repetitive transcranial magnetic stimulation (rTMS), which arguably is the most recommended neurostimulator for treatment-resistant depression (McClintock S, 2018).

Increased scientific research and innovation in the neurological fields have introduced more emerging, novel treatments. As a result, there has been increased pressure on the FDA to modernize its rules for an expedited approval process (Berglund J, 2014). Despite most treatments' regulation under the FDA as Class III medical devices, there is still a public health risk due to the relatively lack of standardization among different treatment types (Krause J, 2018). For instance, some of the dangers posed from lack of standardized policies include potentially unenforced public safety safeguards which are intended to protect and promote public health(Krause J, 2014).

A preliminary search of past literature reviews and relevant research has been conducted by the researcher. Based on such review, findings show a lack of standardized

policies on the regulation of novel and emerging uses of invasive neurotechnological interventions for treatment of mood disorders.

In contrast, there is a more regulatory guidance, as well as FDA approval, for use of noninvasive treatments for mood-related disorders (Shephard R, 2018)(Marjenin T, 2019). Therefore, it is hypothesized that there is arguably little research on utilization, evidence, and other applied areas with invasive neurotechnological treatments. It is also predicted that there is lack of standardized policies and regulations in place, and by extension, no public health safeguards to ensure ethical and effective application of neurotechnological treatments for treating mood disorders.

The abovementioned points to a notable gap in the body of research for neurostimulators, which this scoping review seeks to address. Additional research on the treatment capabilities of invasive neurostimulators, as well as the risks posed by emerging implantable devices, is of value to the scientific community. New research insights on emerging invasive neurostimulators can also help guide better-informed policies, which can benefit the public as well.

Furthermore, the thesis serves to highlight potentially beneficial treatment options for serious psychological conditions. Taking depression as one example, it is estimated to have a "lifetime prevalence of 15 to 20% in the United States [and be] the leading cause of years lost to disability worldwide, and is 1 of the top 3 contributors to global burden of disease." (Filkowski M, 2017). Given the magnitude of mental health conditions, it is imperative to consider the benefits and risks associated with invasive neurostimulators. While noninvasive neurostimulators are approved for treatment in treatment-resistance depression, there is less

opportunities for invasive techniques to be available at treatment options (McGirr, 2018). Reasons for this delta may simply be due to lower amounts of FDA-approved options for invasive treatments and devices. The following is supported by a recent report provided by the FDA's Office of Neurological and Physical Medicine Devices (OHTS) as well as by the 'larger literature' that was reviewed during the scoping review process (Marjenin, T, 2019).

Overall, a scoping review can be helpful to learn more about invasive neurostimulators' capabilities with treating intractable mood disorders. Although still limited in their medical application, further research and evaluation on such practices will be important to conduct. It is the researcher's objective that such scoping review can help evaluate and assess currently available literature on invasive neurotechnological interventions for mood disorders.

Methods

A scoping review will be conducted on select national databases, such as PubMed and Cochrane Database Syst Review. There also may be additional inclusion of other research articles outside of the scoping review which are determined to be relevant enough for consideration. The initial scoping review will be performed with reference to the PRISMA-ScR - checklist (Tricco, 2018). A scoping review was determined as best equipped to explore research on the potential treatment capabilities offered by invasive neurostimulators, specifically for mood disorders. Therefore, data on invasive neurotechnological interventions will be reviewed based on their categorical research area, including but not limited to: type of invasive treatment technique (e.g. DBS or VNS), specific mood disorders, study type, and applicable policies or regulations. Based on the research findings, the thesis will suggest research implications for potential future studies seeking to understand any present research gaps with regards to invasive neurostimulators. In sum, the research question driving the scoping strategy is: What are the regulations or policies for the different types of mood disorders which invasive neurostimulation techniques can treat?

Search Strategy

A comprehensive search strategy is detailed in the Appendix, with a summarization detailed under Table !. Searches were mostly conducted in Jan 24, 2020, and later to recheck in April 2020, in PubMed and Cochrane Database System Review. Examples of search terms included were “Deep Brain Stimulation” or “DBS” or “Vagus Nerve Stimulation” or “VNS” or

"invasive neurostimulation" or "invasive brain stimulation" or "noninvasive brain stimulation" AND in combination of "mood disorders" or "major depressive disorder" or "MDD."

The above query was also repeated for other purposes outside the scoping review, mainly to attain additional background information. This will be done by adding other terms such as "recommendations" or "FDA" or "regulations" or "policies" or "economic evaluation" or "ethical." Synonymous terms and other associated terms were also employed in these searches. Please reference the Appendix, Table I, and Figure ! for additional information on the thesis' search strategy, and other associated scoping review protocol, such as data extraction information.

Inclusion Criteria

Relevant studies which discussed invasive neurostimulation treatments for mood disorders, such as treatment-resistant depression (TRD) or obsessive-compulsion disorder (OCD), were included in the scoping review. Some substance related disorders, such as anorexia nervosa (AN) or cocaine dependence were also included in the scoping review. However, studies which did not specify a particular type of substance abuse or drug addiction was not included. Studies which discussed non-invasive treatments were not included. Inclusion criteria for studies was set by their research design, with most including studies being one of the following: randomized controlled trials (RCTs), evaluation studies, literature reviews, study protocols, and government guidelines. Last, studies before the year 2017 were not included in the scoping review due to time and budget constraints. More supplemental information can be referenced in the Appendix.

Table I: **Summary of Data Extraction Process**

Identification:	**389 Entries**
Excluded:	284
Additional Excluded (via Filtering):	99
Studies Included:	6
*added from individual hand search:	3
Total Studies Included	**9**

**please see Figure 1 and Appendix for more related information

Table II – **Results of Scoping Review**

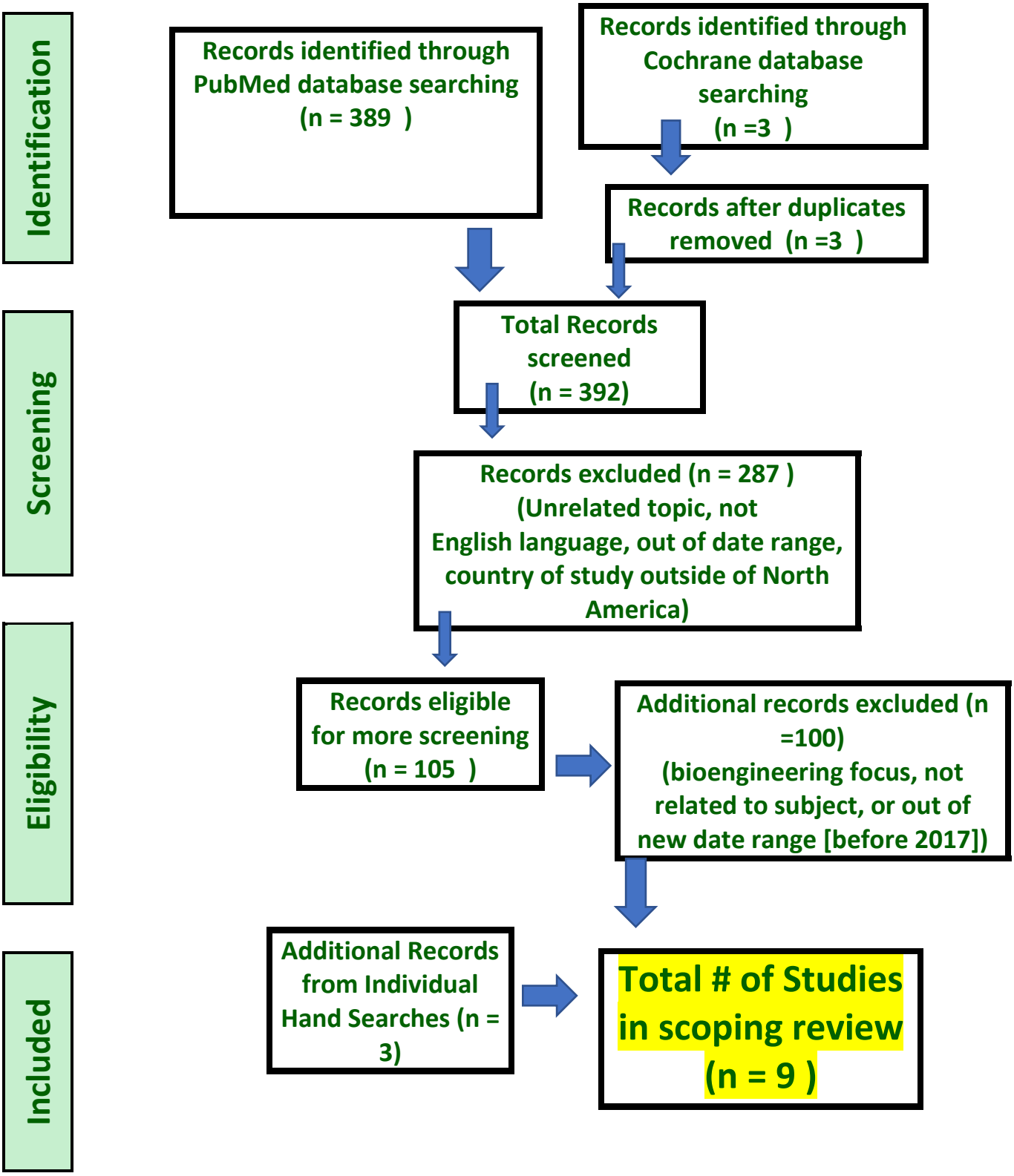
		Aaronson (2018)	Casmari (2018)	Edwards (2018)	Filkowski (2019)	McGirr (2018)	McIntyre(2017)	Milev (2016)	Park (2018)	Rachid (2018)	No. (%) out of a total of 9 Studies
Treatment Type?	DBS		X	X	X	X	X	X	X	X	8 (88.89%)
	VNS	X	X	X		X		X			5 (62.5%)
For Which Conditions?	Treatment-Resistant Depression	X (with both)	X (with VNS)	X (with VNS)	X (with both)	X (with both)	X (with both)	X (with both)			DBS: 5(62.5%); VNS: 7(77.78)*
	OCD		X (with DBS)	X (with DBS)					X (with DBS)		DBS: 3(33.33%)** VNS: 0(0%)
	Anorexia Nervosa								X (with DBS)		DBS: 1(62.5%) VNS: 0(0%)
	Addictions									X (DBS; for Cocaine Dependence)	DBS: 1(11.11%); VNS: 0(0%)
	Type of Study	Review	Review	Review	Review	c meta-review	Medical Guidelines	Guidelines	Study Protocol	Review	

Table III - Important Information on Invasive Neurostimulators

Type of Neuromodulation Technique	Type of Mood Disorder	Regulatory Status
Deep Brain Stimulation	Obsessive-compulsive disorder (OCD)	Indication only; Class IIII (has HIE exemption since 2009)
	Anorexia Nervosa	Limited off-label use; clinical evidence shows potential therapeutic use
	Drug Additions: Cocaine Dependence, Opioid Addiction	Limited off-label use; clinical evidence shows potential therapeutic use
	Treatment-Resistant Depression	Mixed research findings; ongoing clinical trial
Vagal Nerve Stimulation	Treatment-Resistant Depression	Indication only; Class III

*information from Marjenin, T. et al.; Lee, Darrin., et al., etc.

Figure 1 – Charting Data Extraction Process: A Flow Chart



Analysis

The scoping review analyzed 9 studies, as detailed in Table 2. Many dozens of other studies were excluded for variety of reasons, as described in Table I and Figure I. Studies were excluded mostly for three main reasons: 1) published language was not English language or the journal was not in North America, 2) subject area of the research was unrelated to the thesis's objective (e.g. being too focused on the biomedical engineering aspect of devices) and 3) focused on the wrong research areas of the scoping review (e.g. centered around "non-invasive" treatments or movement disorders). Supplemental exclusion criteria were set, which is listed in the Appendix.

7 out of 9 studies in the scoping review (78% of total studies) were literature reviews (from PubMed) that looked at the therapeutic uses of invasive neurostimulators for mood disorders. The remaining 2 studies (22% of total studies) were government issued guidelines concerning safety recommendations. One study was a guideline issued from the federal level in Canada, while the other was at the U.S. state-level (McIntrye, 2018)(Milev, 2016). Looking abroad to Canada, clinical guidelines issued for neurostimulation treatments used for the "management of adults with major depressive disorder", encompassed 6 types of 'neurostimulation modalities' – 4 of the 6 being noninvasive treatments (Milev, RV, 2016). Intriguingly this pattern is the same in the U.S., with the about 4 of 6 of FDA-approved neurostimulators being non-invasive treatments (Marjenin, T, 2019).

Regarding the uses of invasive neurostimulation treatments, the scoping review found invasive neuromodulation treatments to be discussed in 9 of the 9 articles, as having therapeutic use for at least one mood disorder. However, the other 2 out of 9 focused on

addiction related disorders. Overall, there was more emphasis on invasive treatments for certain mood disorders, a recurrent characteristic of those studies which will be discussed in greater detail in the Discussion and Conclusion section.

On another note, FDA approval of an Early Feasibility Studies (EFF) investigational device exemption (IDE) was another indicator which was considered, but ultimately excluded. Per one study, devices for neurological purposes composed of most EFF IDEs (Holmes, D.R; 2017) However, given the limited data from a small sample size of EFF IDEs – which were only available after 2016 (post-passage of the 21st Century Cures Act) – there is not much external validity and so was excluded from the scoping review.

Thus, the majority of reviewed studies were 1) literature reviews on uses of invasive neurostimulators, and 2) specifically for the treatment of mood disorders. The scoping review also highlight noticeable patterns, as detailed in the Appendix and in Table 2. Overall, most studies in the scoping review detailed invasive neurostimulators therapeutic uses in aiding patients with treatment-resistant depression. Depression had the overall highest frequency in being mentioned as a potentially treatable condition by the two main invasive techniques we covered, VNS and DBS. However, Deep Brain Stimulation was more commonly discussed as an intervention option, versus that of VNS. DBS was most covered for its treatment capabilities with depression (5 out of 9 studies mentioning it), then next with ODC (per 3 out of 9 studies). Similarly, vagal nerve stimulation was also mostly commonly cited as an intervention for depression – and overall was the treatment type most mentioned for its therapeutic use with treatment-resistant depression.

Discussion

As discussed, it was noted that non-invasive treatments have historically (and consistently) been used more for treatment-resistant depression by physicians. This is especially true for repetitive transcranial magnetic stimulation (rTMS) in its treatment for depressive disorders(McIntryre, 2018). Meanwhile, invasive treatments have been cited less as treatments for major depression disorder, or in any other severe cases of mood disorders. In fact, invasive neurostimulations are only approved for 2 indications, with DBS devices having a rare HDE exception pertaining OCD and VNS having an indicated use for treatment-resistant depression (Marjenin, T, 2019). Thus, there is a gap between noninvasive and invasive neurostimulators, regarding its use in treating depression and other mood disorders.

The scoping review explored invasive neurostimulation techniques in hopes of adding value to the abovementioned research area. Overall, analysis of the conducted scoping review has thus far shown little information regarding invasive neurostimulation interventions as treatment option for mood disorders. For instance, as detailed in Table II, the majority of both VNS and DBS studies mention their therapeutic use with treatment-resistant depression. However, this is not congruent with our findings for other severe psychological disorders, such as Bipolar Affective Disease, General Anxiety Disorder, and Schizophrenia – which were not substantially discussed in the articles included in the scoping review. Reasons for these findings can be attributed to an array of factors, as discussed in the next section.

Conclusion

Summary of findings

The scoping review did not find an abundance in information on invasive neurostimulators' therapeutic use with treating most cited psychiatric disorders (e.g. Bipolar Disease, Attention Deficit-Hyperactive-Disorder, Bipolar, etc.) as we detailed in our results (Table 2 for results). Treatment-resistant depression was the main exception to this rule, as well as OCD to a limited degree - with most of the included studies covering DBS' promising on-going research with potentially treating TRD and OCD. It is also important to note that VNS is the only invasive neuromodulation technique which is currently FDA-approved for indicated use of TRD (Aaronson, 2018). Hence, most of the reviewed studies on VNS were based off a larger amount of publicly available data, as VNS devices have been in the 'marketplace' longer than DBS for depression (Mertens, 2018).

The current body of research points to the promising returns which VNS and DBS can bring as a last-resort treatment option for intractable mood disorders. There is no doubt about the transformational health improvements which both invasive neurostimulator treatments can yield; however, there should be caution with attempts to prematurely challenge existing regulatory barriers which serve the public health (Loftus C, 2018).

Furthermore, it is argued that the FDA's authority to issue a Class III classification with invasive neuropsychiatric devices is not sufficient enough, given the lack of federal guidelines on invasive neurostimulators therapeutic use in psychiatric disorders (Krause,). One proposed solution is to study the case of two noninvasive neurostimulators' therapeutic use with mood disorders, which interestingly were able to change their regulatory pathway track from a PMA

pathway to a less stringent 501k pathway(Marjenin, 2019). However, the contextual information is uncertain and remains speculative. Even more, advocating for a less stringent approval process is not feasible for invasive neurostimulation devices, which are perceived to be riskier due to their 'implantable' nature (Filkowski, 2017).

Limitations

The scoping review presents limitations in the amount of research it was able to cover, given the relatively lack of FDA-approved invasive neuromodulation devices for mood and anxiety disorder. The following limitation also guided our scoping review protocol with its search criteria for included studies – which had to be based off clinical trials or off-label use collected from 2017-2019. There is also a lack of publicly available data on the utilization trends of invasive neurostimulators, as well as little research focused on either the economic or ethical considerations of their growing research and medical application. While the scoping review identified these limitations, it can also be perceived as future opportunities to guide new and exciting research.

Concluding Remarks and Final Recommendation

The scoping review provides insights on potential roadblocks for further advancing the adoption of new neurostimulation treatments. For instance, there is not much standardized guidelines from regulatory bodies on both approved indications and off-label uses of invasive neurostimulators for mood and anxiety disorders(Stahl, 2018). In addition, not much economic evaluation or cost effect studies were able to be identified in the scoping review, and if they

were, they were exclusively for non-invasive neurostimulation treatments (Niyazoa, 2018)(Voight, 201)(Mendlowitz, 2019).

Hence, future studies can contribute by attempting to conduct an economic evaluation or a cost-effective analysis of treatment types for mood disorders. Understanding the economic factors can be helpful not only to researchers, but also to all stakeholders: including physicians, patients (consumers), and device manufacturers (Rome, 2014). Encouraging further adoption of standardized best practices from more established medical practices can be a valuable best practice to consider as well. This is stressed since non-invasive treatments generally more clinical guidelines and safety recommendations for mood disorders than invasive treatments, which is also another research opportunity for future follow up studies (McClintock, 2018)(Perera, T, 2016).

Another case study worth considering for best practices is the relatively successful adoption of cardiac pacemakers in patient care; thus, improving patient's health and also setting the framework for a new commercially successful market. On a similar note, ensuring all stakeholders involvement in the regulatory approval process, including patients, is paramount to the adoption of novel new neurotechnological intervention(Bergland, 2014).

In sum, the scoping review was able to identify the above areas where there is arguably a need for more research. A final area also recommended for further research are other therapeutic applications of neurostimulators, such as in substance related disorders. As evidenced in the scoping review, there is growing clinical evidence of potentially life-saving benefits which deep brain stimulation can have with treating patients afflicted with cocaine dependence and other drug addictions. One therapeutic use for DBS can be with helping

individuals who are combating with Opioid Addiction. Further research and funds should invest in our efforts to combat this public health crisis – which can potentially be lifesaving for many thousands in the United States (Bernstein L, 2019).

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Appendix A - Supplemental Information for Scope Review

PubMed Search – Search 1:

		# of Included Studies
Initial Query:	("substance-related disorders"[MeSH Terms] OR "mood disorders"[MeSH Terms] AND "neurostimulation"[tw]) OR "invasive brain stimulation"[mh])	60 studies
Additional Filters to include:	AND (Review[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb] OR Practice Guideline[ptyp] OR Guideline[ptyp] OR Evaluation Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "last 5 years"[PDat] AND English[lang] AND (systematic[sb] OR Review[ptyp] OR Guideline[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Evaluation Study[ptyp]) AND ("2017/01/01"[PDat] : "2019/12/31"[PDat]) AND English[lang]	17 studies
Modify Filter for more screening:	Change "*AND last 5 years"[PDat* with *"AND ("2017/01/01"[PDat] : "2019/12/31"[PDat])"*	10 entries
removed 8 studies from failing to meet eligiblity		2 studies (Aaronson)(Rachid)

PubMed Search – Search 2:

		# of Included Studies
Initial Query:	*(mood disorders[mh] OR substance-related disorders[mh]) AND ("vagus nerve stimulation"[tw] OR "invasive brain stimulation"[mh])*	201 studies
Additional Filters to include:	*AND (Review[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb] OR Practice Guideline[ptyp] OR Guideline[ptyp] OR Evaluation Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "last 5 years"[PDat] AND English[lang]*	39 studies
Modify Filter for more screening:	Change "*AND last 5 years"[PDat* with *"AND ("2017/01/01"[PDat] : "2019/12/31"[PDat])"* **201 entries -> 39 -> 26 = 1**	26 entries
removed 25 studies from failing to meet eligiblity		**1 study (McGirr)**

PubMed Search 3:

		# of Included Studies
Initial Query:	*substance-related disorders[mh] OR mood disorders[mh]) AND "neuromodulation"[tw] OR "invasive brain stimulation"[mh])*	128 studies
Additional Filters to include:	*AND (Review[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb] OR Practice Guideline[ptyp] OR Guideline[ptyp] OR Evaluation Study[ptyp]) AND "last 5 years"[PDat] AND English[lang]*	49 studies
Modify Filter for more screening:	Change "*AND last 5 years"[PDat* with *"AND ("2017/01/01"[PDat] : "2019/12/31"[PDat])"*	33 entries
removed 30 studies from failing to meet eligiblity		**3 studies (Casmari)(Filkowski) (McIntyre)**

Deviation from scoping protocol:

*added from individual searches using disembogues terms and "similar articles" tabs on above searches: **3 (Milev, Park, Edwards)**

Cochrane System Review:

MeSH Terms: Neuromodulation OR Invasive brain stimulation OR Deep brain stimulation OR DBS or Vagal nerve stimulation OR VNS

3 systemic reviews were identified, but all 3 were excluded as they did not fit the inclusion strategy (were for movement conditions)